AP1-08043: The Accelerated Development of Monoclonal Antibody UC-961 For Eradication of Cancer Stem Cells

SCORES AND RECOMMENDATIONS

Score: <65
GWG Recommendation: Not recommended for funding

Public Abstract (provided by applicant)
This application is for supplemental funding to accelerate clinical development of UC-961 (cirmtuzumab), a fully-humanized monoclonal antibody that binds to the extracellular domain of ROR1, which is a surface protein expressed on embryonic cells and cancer cells. ROR1 is not expressed on normal adult tissues. However, ROR1 is highly expressed on the surface of chronic lymphocytic leukemia (CLL) cells and on cancer stem cells (CSC), which account for the drug-resistance, relapse, and metastasis of many cancers. Because UC-961 is highly specific for ROR1, it does not bind normal adult tissues, but instead binds tightly to CLL cells and to CSC. Treatment of CLL cells or CSC with UC-961 inhibits the proliferation, migration, survival, and metastatic/engraftment potential of CSC. Moreover, UC-961 may eradicate CSC while sparing stem cells of normal tissues, potentially providing for a revolutionary, highly-specific, and effective anti-cancer therapy.

Under the auspices of a CIRM Disease-Team 3 Award, we will conduct a phase I/II study to determine the safety, tolerability, and activity of UC-961 in patients with CLL. Supplemental funding will allow for assays on leukemia cells of patients before, during, and after therapy with UC-961 to examine for treatment-induced effects that may correlate with clinical outcome. Also, these assays may define new biomarkers that can identify patients who most likely will benefit from UC-961 anti-CSC therapy. Finally, supplemental funding will allow another clinical site to activate this trial to accelerate patient accrual.

Supplemental funding also will allow us to initiate follow-on phase I clinical trials for patients with pancreatic adenocarcinoma or ovarian cancer with protocols cross-filed under our IND for UC-961. These studies will determine the safety, tolerability, and potential activity of UC-961 in patients with ROR1+ CSC-driven, solid-tissue cancers. These studies will incorporate biomarker studies and imaging assessments to define a clinical proof of concept and to inform decisions for subsequent pivotal clinical testing on a registration pathway. In addition, these studies will incorporate correlative studies on primary-cancer-derived xenografts, primary cancer cells, or blood samples of treated patients, testing the activity of UC-961 alone or in combination with other active anti-cancer drugs (e.g. gemcitabine in pancreatic cancer, platinum and taxane in ovarian cancer). These studies may identify treatment effects that correlate with clinical outcome and identify subsets of patients who most benefit from treatment with UC-961 for further examination.

Statement of Benefit to California (provided by applicant)
Cancer is a leading cause of death for Californians. Thousands of adults and children in California succumb to cancer relapse following treatment with surgery, radiation, and/or conventional chemotherapy. Although gains have been made in the treatment of some cancers, over 50% of adults diagnosed with leukemia will die of their disease. The outlook for patients with many solid-tumor cancers is even worse, particularly for those patients with tumors having poorly differentiated, high-grade malignancies, which have an increased propensity for metastases and/or early relapse after therapy. Nonetheless, current therapies can cost several tens of thousands of dollars per patient per year, factor in cancer-related depression, and do not cure the disease. For the physical, mental, and financial health of the citizens of California, we need to find curative treatments for patients with cancer.

What has held up progress toward a cure? Compelling evidence indicates that the leukemias and many solid tumors are not curable because most treatments do not destroy small numbers of multi-drug resistant cancer stem cells (CSC); dormant cancer stem cells (CSC) provide for the drug-resistance, relapse, and metastasis of many cancers. Required are agents that can eradicate CSC while sparing the vital stem cells of normal tissues.

This project will fund clinical development UC-961 (cirmtuzumab), a fully-humanized monoclonal antibody that binds an extracellular epitope of ROR1, which is an onco-embryonic antigen. While ROR1 is not expressed on normal post-partum tissues, it is highly expressed on the surface of chronic lymphocytic leukemia (CLL) cells and on cancer stem cells (CSC). Because UC-961 is highly specific for ROR1, it does not bind normal adult tissues, but instead binds tightly to CLL cells and to CSC. Treatment of CLL cells or CSC with UC-961 inhibits the proliferation, migration, survival, and metastatic/engraftment potential of CSC. As such, UC-961 may eradicate CSC while sparing stem cells of normal tissues. Such studies may lead to the potential commercialization of UC-961, which could provide a

revolutionary new form of anti-cancer therapy for Californians with intractable malignancies.

In summary, the benefits to the citizens of California from the CIRM disease specific grant in cancer are:
(1) direct benefit to the thousands of leukemia and solid-tumor cancer patients
(2) financial savings due to effective treatments that may eradicate CSC and obviate current therapies that are less clinically active and/or cost-effective

REVIEW SUMMARY
The applicant is developing a therapeutic antibody candidate that can kill cancer cells and cancer stem cells that express a specific cell surface protein. While typically absent on healthy adult cells, activation of this protein promotes survival, proliferation and migration of cancer cells. The cellular pathway activated by the protein is stimulated in over 90% of people with chronic lymphocytic lymphoma (CLL). In the Parent Award, the applicant has proposed a Phase 1a/b clinical trial in patients with CLL to identify a safe and efficacious dose of the therapeutic antibody. In June 2014, the applicant's IND was approved by the FDA to begin the first in human clinical trial in CLL. In this application, additional funds were requested to add 1) new bioassays and an additional trial site to the funded Phase 1a/b clinical trial in CLL, and a Phase 1b re-treatment trial in CLL; 2) a Phase 1 clinical trial in pancreatic cancer; and 3) a Phase 1 clinical trial in ovarian cancer.

Clinical Competitiveness and Impact of the Proposed Therapy
- Although CLL is a highly competitive area, reviewers were very enthusiastic about the candidate therapeutic, describing it as a highly novel target with the potential to be a first in class antibody therapy for CLL.

- Pancreatic and ovarian cancers have great unmet medical need, but reviewers were less convinced by the data provided that the therapeutic candidate under development could have significant benefit in these cancers.

Strength of the Development Program
- Reviewers commented that reasonable contingency plans have been made to address potential clinical challenges in the CLL Phase 1a and, if needed, Phase 1b trials.

- Reviewers noted that the development/regulatory path for a monoclonal antibody therapeutic is well-defined, which will benefit the team's program progress.

- A major strength of the project is the growing pharmaceutical/industry interest in the candidate therapeutic, and the team was encouraged to continue seeking discussions with potential partnering groups (update since the GWG review, the applicant finalized a collaborative agreement with an industry partner in August).

Qualifications of Development Team
- Reviewers described the team as highly qualified to complete the proposed studies. The PI is a recognized leader in the field of CLL and other members of the team have experience in hematological malignancies and solid tumor oncology.
Progress on Parent Award and Effective Program Leadership
- The Parent Award is focused on CLL as a first clinical indication and has a high probability for success. The team is making timely progress and has effectively incorporated changes to reflect regulatory input.

- Reviewers were encouraged by the team's progress on establishing correlative biomarker assays, which may be highly relevant for future development of the therapeutic candidate and selection of the most appropriate patient populations for treatment.

Relevance of the Therapeutic to Regenerative Medicine
- The therapeutic candidate antibody recognizes a cell surface protein that is expressed on cancer cells and cancer stem cells.

- If initial clinical studies demonstrate significant cytotoxic effects of the candidate therapeutic on cancer stem cells, reviewers agreed that it could help prevent drug resistance, metastasis and relapse in a number of cancers.

Proposed Activities for Acceleration of the Development Program
- Reviewers described the follow-on clinical activities proposed for the CLL trial as "logical," but unlikely to accelerate the overall development time line toward demonstration of clinical proof of concept for CLL.

- While the reviewers appreciated the value of extending the Development Program to additional clinical indications, they did not think that adding additional Phase 1 trials at this time would sufficiently advance the team's progress to demonstration of clinical utility for the therapeutic candidate.

Feasibility of Proposed Activities for Acceleration of the Development Program
- The Phase 1b retreatment trial for CLL that was proposed would provide valuable long-term safety and efficacy data at the targeted Phase 2 dose. While reviewers felt the study was important and appropriate , they did not think it could be initiated until quite late in the activities conducted under the Parent Award, given the lengthy time proposed to complete the Phase 1a component, and would be unlikely to accelerate overall progress. The reviewers strongly encouraged the applicant to consider ways to accelerate the completion of the Phase 1a component e.g., adding more clinical sites.

- The team noted that the therapeutic candidate could be more potent in some tumor types than in others; reviewers questioned how informative the dosing information gained from the CLL trials would be for expansion of the therapeutic to other clinical indications. Overall, the reviewers thought the highest probability of success would be in CLL, and thought CLL should remain their primary focus to establish proof of concept.

- Reviewers encouraged the team to reconsider the clinical endpoints proposed for the pancreatic and ovarian cancer trials to maximize the functional information that could be gained from these studies.

- Reviewers questioned whether proposed studies that would require comparison of solid tumor samples collected pre-treatment to post-treatment samples would be limiting for patient recruitment and selection.

Conflicts:
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